IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mamchur *

Serial No. 10/668,075 *

Filed: September 22, 2003 *

Art Unit: 1616

For: A SYSTEM FOR USE BY COMPOUNDING PHARMACISTS TO PRODUCE HORMONE REPLACEMENT MEDICINE CUSTOMIZED FOR EACH CONSUMER *

Examiner: Nathan W. Schlientz, Ph.D.

*

REQUEST FOR ENTRY OF THE
SECOND DECLARATION BY STEPHEN A. MAMCHUR

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant requests that the new expert Declaration by Dr. Stephen Mamchur enclosed with this Request be entered into the patent application file pursuant to 37 CFR §§41.33 (d)(l) and 1.116(e), on the basis that there are good and sufficient reasons why the affidavit is necessary and was not earlier presented. This Declaration addresses issues raised by the Examiners during the Interview at the U.S. Patent Office on May 12, 2010.

June 10, 2010
Date

Respectfully submitted,

Robert M. Gamson
Reg. No. 32,986
Attorney for Applicant

HODES, PESSIN & KATZ, P.A.
901 Dulaney Valley Road, Suite 400
Towson, MD 21204
Phone: 410-769-6145
Fax: 410-832-5637
E-Mail: rgamson@hpklegal.com

CERTIFICATE OF TRANSMITTAL

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: June 10, 2010
Express Mail Label No. EH033511435US

By: Carolyn H. Bates
Carolyn H. Bates

RMG/chb
G:\files\GAMSON\MAMCHUR, Steven (Blaney McMurtry LLP)\025357.001\PTO Request Entry 2nd Declaration.docx

OPAP IAP6
JUN 10 2010
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Stephen A. Mamchur

Filing Date: September 22, 2003

Serial No: 10/668,075

Docket: 025357.001; 097928-0001

Title: A SYSTEM FOR USE BY COMPOUNDING PHARMACISTS TO PRODUCE HORMONE REPLACEMENT MEDICINE CUSTOMIZED FOR EACH CONSUMER

Art Unit: 1616

Examiner: Nathan W. Schlientz, Ph.D.

SECOND DECLARATION UNDER 37 CFR § 1.132
STEPHEN A. MAMCHUR

Commissioner for Patents
Alexandria VA 22313

I, STEPHEN MAMCHUR, do hereby declare as follows:

I came to the Patent Office on May 12, 2010, and demonstrated my invention to Examiner Nathan W. Schlientz, Examiner Johann Richter, Examiner John Pak, and Examiner Johnny Railey.

At the interview, the Examiners asked whether concentrated solutions of estrogen could be prepared in solvents other than ethoxy diglycol and propylene glycol mixed at a 1:1 ratio.

General solubility of estrogen in polar aprotic solvents

Enclosed with this declaration is Product Information obtained from Cayman Chemical. They are a chemical supply company that sells over 1,000 products for use in medical research. The information sheets state the following:

- β-estradiol is soluble in ethanol (CH_3-CH_2-OH) at 2.5 mg/mL, in dimethyl sulfoxide (CH_3-S(=O)-CH_3) (DMSO) at 20 mg/mL, and in dimethyl formamide (H-C(=O)N(CH_3)$_2$) (DMF) at 20 mg/mL.
- Estrone is soluble in DMSO at 20 mg/mL, and DMF at 20 mg/mL.
- Estriol is soluble in ethanol at 5 mg/mL, DMSO at 20 mg/mL, and DMF at 30 mg/mL.

DMSO and DMF are polar aprotic solvents. This means that there is a charge separation within the solvent molecule, but no dissociable H^+ attached to an anionic atom. It makes sense that these estrogens are soluble in polar aprotic solvents like DMSO and DMF, because they have a cholesterol-like structure with two or three oxygens in the form of ketone and/or hydroxyl groups.

Estrogens are also soluble in mixtures of Transcutol® (diethylene glycol monoethyl ether) and propylene glycol monolaurate (PGML) up to about 50 mg/mL, as demonstrated in Example 6 of the PCT patent application from Cygnus Research Corporation (WO 90/11064).

The therapeutic range for dermal administration of estrogens is about 0.325 to 5.0 mg/mL, with 0.625, 1.25 or 2.5 mg/mL being typical. Clearly, there are several solvents that can be used to prepare concentrated solutions of estrogen well above the therapeutic range

Solubility in mixtures of ethoxy diglycol and propylene glycol

To determine solubility in ethoxy diglycol and propylene glycol, I had my technicians do the following experiment. A 10 mL volume of each solvent mixture was prepared, and set in a beaker with a magnetic stir bar on a hot plate. 50 mg of estriol (estra-1,3,5(10)-triene-3,16α,17β-triol) was added (i.e., 5 mg per mL solvent). When the first 50 mg was dissolved, another 50 mg was added. This was repeated until the solution became murky. If the murkiness did not clear after 5 min, then the total amount of estrogen up to but not including the final addition was considered to demonstrate the saturation point.

The following results were obtained:

Ratio of ethoxy diglycol : propylene glycol (vol : vol)	Amount of estriol dissolved
1:3	40 mg per mL solvent
3:1	35 mg per mL solvent
1:2	30 mg per mL solvent
2:1	35 mg per mL solvent
1:1	45 mg per mL solvent

The combination of ethoxy diglycol and propylene glycol at a 1:1 ratio dissolved somewhat more estrogen than the other mixtures tested. Still, my discovery that ethoxy diglycol and propylene glycol work well together to dissolve estrogen stays true when the solvent ratio is varied over a wide range.

Choice of solvent

As we said at the interview, there are several different solvents and solvent combinations that would provide concentrated estrogen solutions suitable for making custom tailored pharmaceutical products for hormone replacement therapy, as described in my patent application.

In my expert opinion, the ethoxy diglycol : propylene glycol combination provides important advantages in relation to the other solvent systems referred to in this Declaration. Ethoxy diglycol and propylene glycol are both essentially innocuous solvents that create stable and long-lasting estrogen concentrates. On the other hand, some polar aprotic solvents like DMSO are less preferable when present in pharmaceutical preparations at large concentrations, because they can leach dye out of clothing and may promote penetration of dye through the skin. PGML is a long-chain fatty acid ester, and there may be stability and storage issues.

Thus, my invention has several components. One part is the overall pharmaceutical compounding system, which can be set up for the pharmacist using any one of several different solvents for each of the concentrated reagents. Another part of my invention is the ethoxy diglycol : propylene glycol combination as a particular estrogen solvent having certain advantages. A third part of my invention is the color coding system that ensures correct choice of reagents and complete mixing of each custom tailored product made by the pharmaceutical technician.

Units of the combination

Examiner Schlientz has also raised the question of what was meant when the text of the application refers to "a mixture of 50% ethoxy diglycol/50% propylene glycol".

A pharmacist or pharmaceutical manufacturer reading this description would understand this to mean that equal volumes of the two solvents were mixed together. Based on what appears in the description, a pharmacist or pharmaceutical manufacturer would make the combination by measuring each of the solvents using a graduated cylinder, pipette, or similar volume measuring device, rather than weighing them on a balance.

In any event, there is little practical difference between a 50:50 (vol/vol) mixture and a 50:50 (wt/wt) mixture of the two solvents. The density of ethoxy diglycol is about 0.99 g/cm^3, while the density of propylene glycol is about 1.036 g/cm^3. Thus, a 50:50 (wt/wt) mixture of the two solvents would be about a 51:49 (vol/vol) mixture. As shown above, the ability of the solvent mixture to dissolve estrogens is not critically dependent on the exact ratio of the two solvents used.

I hereby declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true: and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

7/June/2010 _____

Date

STEPHEN A. MAMCHUR, B.S.P.
Calgary, Alberta, Canada